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DATA EVALUATION REPORT

Study Type: 83-5 - Combined Chronic Toxicity/Oncogenicity - Rat

TOX Chem No.: 63AB

MRID Nos.: 400696-01, Vol. 1-11; 405178-01, Vol. 1 and 2; 403755-11

Accession No.: N/A

Test Material: Abamectin

Synonyms: Avermectin B_1, MK-0936

Study Number(s): TT#82-099-0

Sponsor: Merck and Company

Testing Facility: Merck Sharp and Dohme Research Labs

Title of Report: One-Hundred and Five-Week Dietary Carcinogenicity and Toxicity Study in Rats.

Author: L. Gordon

Report Issued: August 27, 1985

Conclusions:

The oncogenic potential was negative up to 2.0 mg/kg/day (HDT). The high-dose is also considered to be the MTD. The systemic no-observed-effect level is 1.5 mg/kg/day, the mid-dose. The lowest-effect level is 2.0 mg/kg/day and the effects were treatment-induced tremors in both sexes. An additional female in the mid-dose group also had tremors, but this animal consumed about 2.5 mg/kg/day of abamectin during this period (based on actual food consumption and body weight data). There were no compound-related pathological lesions to correlate with the tremors.

Classification: Core-Minimum

Special Review Criteria (40 CFR 154.7): N/A

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Review:

- One-Hundred-and-Five-Week Dietary Carcinogenicity and Toxicity Study in Rats with MK-0936; Final Report; Merck Sharp & Dohme Research Labs.; TT#82-099-0; August 27, 1985 by L. Gordon (MRID No. 400696-01, Vol. 1-11; 405178-01, Vol. 1 and 2; 403755-11).

Test Material - MK-0936, abamectin, Lot No. L-676, 863-00V54; purity: 91.1 percent.

Animals - Outbred albino rats, Crl:CD (SD) BR, approximately 5 weeks old at initiation, were used in the study. The rats were obtained from Charles River Laboratories, Wilmington, MA. At initiation, males weighed 115 to 191 gm, and females weighed 93 to 154 gm.

The rats were housed in individual cages and were fed Purina Certified Rodent Chow and water ad libitum. Food was withheld approximately 17 hours prior to bleedings and interim and final necropsies.

Methods:

Randomized groups of 65 male and 65 female Sprague-Dawley rats were fed test diets containing 0 (control I), 0 (control II), 0.75, 1.5, and 2.0 mg/kg/day of abamectin. The levels of abamectin in the feed were adjusted and mixed biweekly to attain the targeted dose levels. The vehicle used was acetone which was subsequently dried off. Doses were selected on the basis of results of a range-finding study (TT#82-075-0, -1).

In the 8-week range finding study, the dietary doses were 5, 10, 15, 20, 40, and 60 ppm. Tremors and death were observed in the 40 and 60 ppm groups, as were dose-related decreases in body weight. The tremors began on day 2 and on day 5 the 60 ppm group was terminated. Tremors persisted in the 40 ppm group. Ten animals of the 40 ppm group died by days 3 to 5. The body weight decreases ranged from 5 to 15 percent in the 15 to 40 ppm groups. The intake of abamectin at 40 ppm, ranged from 4.1 to 5.8 mg/kg/day for both sexes. Based on the results of this range-finding study and the results (see below) of the chronic rat feeding study, the HDT of 2.0 mg/kg/day in the chronic rat study is considered the MTD.

Since no effects attributable to test material were observed after 10 weeks, the high-dosage level was increased to 2.5 mg/kg/ day to establish a maximum tolerated dose (MTD). However, due to the appearance of severe signs of CNS toxicity (tremors and death) following the increase in dosage, the dose level for the high-dose group was decreased back to 2.0 mg/kg/day in week 13 for the remainder of the study.

Fifteen animals/sex/group were selected for the 53-week interim sacrifice prior to study initiation.

The total number of days on test was 729 to 733 for males and 729 to 731 for females.

Test diets were prepared every 2 weeks and were used up within 4 weeks. Stability of test material in diets was determined to be satisfactory over a period of 4 weeks at room temperature. Homogeneity of samples from the top, middle, and bottom of each batch was acceptable. Concentrations of test material were determined in duplicate samples from each biweekly dietary batch. Test material consumed by the rats (on a mg/kg/day basis) was generally within 10 percent of targeted levels.

All animals were observed daily for toxic signs and were given detailed physical examinations weekly.

Body weights were recorded at pretest and weekly for all animals throughout the study. Food consumption was measured weekly over a 6-day interval for 12 animals/sex/group.

Ophthalmic examinations were done on all animals at pretest; high-dose and control animals only in weeks 26, 52 (males), or 53 (females), 76 and 102 (males), or 103 (females).

Hematologic examinations were conducted on 10 animals/sex/group at weeks 12, 25, 38, 51, 78, and 105. Beginning in week 89, all early sacrifice animals were bled for hematological examination.

The following hematological parameters were measured - Hg, RBC, WBC, differential WBC, MCV, clotting time, platelet count, erythrocyte sedimentation rate, hematocrit, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

The following biochemical parameters were measured - Glucose, BUN, albumin, total protein, creatinine, SGPT, SGOT, bilirubin (direct and total), SAP, cholesterol, triglycerides, Na, K, Ca, and Cl.

Urinalyses were conducted on 10 animals/sex/group at weeks 12, 25, 38, 40, 51, 78, and 103. Urine was collected overnight from rats placed in metabolism cages. Animals did not have access to feed during the urine collection interval. The parameters measured were microscopic examination of sediment, glucose, protein, bilirubin, and occult blood.

For all early deaths or early sacrifices of moribund animals, all rats had a complete necropsy examination. Terminal body weights but not organ weights were recorded. All tissues,

except testes from early sacrifice males which were fixed in Bouin's fixative, were fixed in neutral buffered formalin.

All remaining rats at the time of scheduled sacrifice were killed by exsanguination after ether anesthesia. All rats had a complete necropsy examination. All tissues were fixed in neutral buffered formalin except for the testes, which were fixed in Bouin's fixative.

Terminal body weights and the following organ weights were recorded: heart, liver, brain, adrenals, kidneys, spleen, and testes. In addition, the following organ weights were recorded at the final sacrifice (at 105 weeks) salivary glands, lungs, thyroid, pituitary, prostate, seminal vesicles, ovaries, and uterus.

Histopathology - Hematoxylin and eosin-stained sections of the left eye (including optic nerve), heart, liver, kidneys, spleen, mesenteric and cervical lymph nodes, pancreas, stomach, small and large intestines, pituitary, adrenals, urinary bladder, thyroid and parathyroid (if present in the section), lung, thymus, salivary gland, bone including joint and bone marrow, brain (3 levels), spinal cord (2 levels), sciatic nerve, testes including epididymides, prostate or ovaries, uterus, skeletal muscle, skin and mammary gland (if present in the skin section) from: (1) the 53-week group: 15 males and 15 females from the control I group and 15 males and 15 females from the highest dosage level and all early death rats in the control II, middle-, and low-dose groups; and (2) all rats in all groups assigned to the 105-week part of the study. Gross lesions were examined from rats in all dosage groups. Statistical analyses of the data were performed.

Results:

Compound-related whole body tremors and overall unthrifty appearance were observed in a few rats in the 2.0 mg/kg/day group.

This effect (tremors) appeared in animals #82-7741F, 82-7742M, and 82-7692M in week 12, which correlated with the increase in dosage from 2.0 to 2.5 mg/kg/day in weeks 11 and 12. The tremors persisted intermittently until the time of sacrifice, despite the reduction in the high-dose level back to 2.0 mg/kg/day in week 13. Additional instances of tremors were observed in animals #82-7691F, 82-7667F, and 82-7713F, all of the high-dose group, beginning in weeks 9, 98, and 65, respectively. The tremors persisted for several weeks until the animals were sacrificed or found dead.

In the mid-dose group, animal #82-7491F developed tremors in week 62 which persisted until the animal was found dead at week 100. Analysis of the food consumption and body weight data

for this animal indicated that this female generally consumed about 2.5 mg/kg/day of abamectin during the interval the tremors were observed. Therefore, tremors were not considered to be an effect of the test material at a dose level of 1.5 mg/kg/day.

The following summary shows the time period between the appearance of tremors and the death of the rats:

Animal No.	Dose	Week of Tremors	Week of Death
7691F	High	9	11
7741F	High	12	53
7742M	High	12	98
7692M	High	12	42
7667F	High	98	100
7713F	High	65	69
7491F	Mid	62	100

Additionally, there were no gross or histopathological lesions in examined nervous tissue or muscle of the rats which could be associated with the tremors. The testing laboratory noted that tremors had also been observed in other species, also without pathological lesions.

The tremors observed in the high-dose group (2.0 mg/kg/day) were considered compound-related. The NOEL for tremors in this study was 1.5 mg/kg/day.

No compound-related effects on survival were noted. Although survival in female control group II was higher than in the treated groups, the survival of females in control group I and the treated groups was similar (see table below).

In male rats, although survival was slightly lower in the high-dose group, the group mean survival times were comparable in the controls and treated groups. The slight decrease in survival in the high-dose group was not considered compound-related.

The table below, as presented in the report, shows the summary of survival in the study.

	Dose (mg/kg/day)									
	Control I		Control II		0.75		1.5		2.0	
	F	M	F	M	F	M	F	M	F	M
No. Starting	65	65	65	65	65	65	65	65	65	65
No. Removed	0	0	0	0	0	0	0	0	0	0
53-Week Sac.	15	15	15	14	14	15	15	14	15	14
No. Found Dead	14	15	3	11	11	17	12	8	12	13
No. Sacrificed	17	11	21	15	23	14	21	13	20	21
No. Survivors	19	24	26	25	17	19	17	30	18	17
Group Survival (Weeks) Mean	82.1	83.0	83.3	84.8	81.0	82.6	80.5	84.9	80.4	79.4

Body weight was increased for both male and female treated rats in all treated groups in comparison to controls.

This effect (increased body weight) has been observed in other studies with abamectin and is considered to be a compound-related effect. Graphs presenting the body weight data in this study are attached.

For the first 76 weeks of the study, body weight of treated female rats exceeded those of the control. The greatest increases occurred at week 60 and were 23, 10, and 9 percent for the low-, mid-, and high-dose groups, respectively, in comparison to the combined controls. Beginning at week 77, the control groups exceeded the treated groups in weight gain, so that at week 104, the average body weights of female rats were 507, 550, 532, 510, and 531 g for the control I, control II, low-, mid-, and high-dose levels, respectively. The overall weight gains for the entire study were comparable for control and treated female rats. These gains were 388, 429, 413, 390, and 409 g for the control I, control II, low-, mid-, and high-dose groups, respectively.

In male rats, the body weight of treated rats exceeded the controls during the entire study. At week 104, the average body weights of male rats were 762, 768, 893, 825, and 797 in control I, control II, low-, mid-, and high-dose groups, respectively. These increases were 21, 9 and 6 percent for the low-, mid-, and high-dose groups, respectively, in comparison to the combined controls. The overall weight gains for the entire study were 610, 614, 742, 668, and 647 g for control I, control II, low-, mid-, and high-dose groups, respectively.

Although these increases in body weight for the male and female rats at all treatment levels are considered to be a compound-related effect, they are not considered to be an adverse toxicological effect and will not be used for the purpose of determining the NOEL for this study or for determining an ADI for abamectin.

Food consumption (gm/day) was comparable between control and treated groups of both sexes during the study. The total mean food consumption for female rats was 22.8, 22.6, 23.4, 23.2, and 23.6 gm/day for control I, control II, low-, mid-, and high-dose groups, respectively. For male rats, the total mean food consumption was 28.0, 27.7, 29.4, 29.2, and 29.0 gm/day for the control I, control II, low-, mid-, and high-dose groups, respectively.

Food consumption, expressed as gm/kg bwt, was comparable between control and treated rats of both sexes during the study.

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105 WEEK DIETARY CARCINOGENICITY AND TOXICITY STUDY IN RATS WITH A 53 WEEK INTERIM NECROPSY
AVERAGE BODY WEIGHTS (GRAMS) FOR MALE RATS
GRAMS

Feed efficiency (body weight gain/amount of food consumed) was slightly increased for low-dose females during the first half of the stuoy in comparison to controls and other treated groups. Thereafter, the feed efficiency declined in the low-dose group to levels comparable to all female groups. The total mean percent of feed efficiency for female rats for the entire study was 2.7, 2.4, 2.3, 2.2, and 2.3 percent for the control I, control II, low-, mid-, and high-dose groups, respectively.

Feed efficiency for male rats was comparable between control and treated groups during the study. The total mean feed efficiency for male rats was 3.0, 3.0, 2.8, 3.0, and 2.7 percent for the control I, control II, low-, mid-, and high-dose levels, respectively.

Average consumption values of MK-0936 for female rats varied during the study between 0.5 to 0.9, 1.2 to 1.7, and 1.6 to 2.5 mg/kg/day for low-, mid-, and high-dose groups, respectively. The mean intake for the entire study was 0.8, 1.5, and 2.1 mg/kg/day for the female rats in low-, mid-, and high-dose groups, respectively.

In male rats, average consumption values for MK-0936 varied during the study between 0.6 to 0.9, 1.4 to 1.7, and 1.8 to 2.8 mg/kg/day for low-, mid-, and high-dose groups, respectively. The mean intake for the entire study in male rats was 0.7, 1.5, and 2.0 for low-, mid-, and high-dose groups, respectively.

Ophthalmological examinations of controls and high-dose male and female rats in weeks 26, 52 (males), or 53 (females), 76 and 102 (males), or 103 (females) did not reveal any compound-related lesions. The most commonly observed lesions which occurred at comparable incidences in control and treated rats included conjunctivitis, corneal scar, anterior and posterior synechia of the iris, posterior subcapsular cataracts, focal retinopathy, and retinal degeneration.

There were no compound-related effects in hematological parameters measured at weeks 12, 25, 38, 51, 78, and 105 weeks in male and female rats. Average values for hematologic parameters in control and treated females were within normal ranges and there were no significant dose-related decreases or increases with time. Similarly, in male rats, most average values for hematological parameters for control and treated rats were within normal ranges and there were no significant dose-related decreases or increases with time. A slight exception to this finding was the average absolute value of 466 nonsegmented neutrophils/mm^3 for the males of the 1.5 mg/kg/day group at week 78. Usually, individual values varied from 0 to 400 for nonsegmented neutrophils in control and treated male rats during the study. However, male rat #82-7574 of the 1.5 mg/kg/day group at week 78 had a value

of 4116 cells/mm^3. This rat had metastatic granulocytic leukemia (primary site undetermined) and was killed moribund in week 92. The tumor was not considered compound-related. Additionally, the increase in average nonsegmented neutrophils was not dose-related and did not occur at week 105 in the remaining rats.

There were no treatment-related effects in serum biochemical parameters measured at weeks 12, 25, 38, 51, 78, and 105 in male and female rats. However, average BUN and creatinine values were increased for low- and high-dose females in week 78, low-dose females in week 105, and high-dose males in week 105. Evaluation of individual animal data showed that in females at week 78, animals #82-7457 (low dose), #82-7571 (mid-dose), and #82-7705 and #82-7711 (high dose) had fourto elevenfold increases in BUN and creatinine elevenfold as compared to controls (58 to 145 mg/100 mL for BUN and 2.2 to 4.4 mg/100 mL for creatinine as compared to normal values for BUN of 10 to 20 mg/100 mL and creatinine of 0.6 to 1.0 mg/100 mL). All these female animals had chronic nephritis (severe), which is a common finding in aged rats.

Additionally, the increases in average BUN and creatinine values in low-dose females and high-dose males at week 105 were due to two females and one male. Females #82-7407 and #82-7409 of the low dose had BUN values of 65 and 63 mg/100 mL and creatinine values of 2.0 and 4.0 mg/100 mL, respectively. High-dose male animal #82-7632 had a BUN value of 370 mg/100 mL and a creatinine value of 8.9 mg/100 mL. Histopathological examination of these animals showed that the low-dose females had marked chronic nephritis and the high-dose male had moderate pyleonephritis.

At week 78, average glucose, protein, cholesterol, and triglyceride values of low-dose females were elevated. These increases were due to female animal #82-7441, which had a glucose value of 645 mg/100 mL, a protein value of 19.40 gm/100 mL, a triglyceride value of 9400 mg/100 mL, and a cholesterol value of 695 mg/100 mL. The blood chemistries were repeated within 7 days for this animal and the values were still elevated. Animal #82-7441 was an unscheduled death at week 92 and had a partially necrotic stomach and liver and a mammary fibroadenoma.

Urinalyses did not reveal any compound-related effects in male and female rats during the study.

There were no compound-related effects in organ weights, gross necropsy findings, or histopathology in male or female rats.

At the 53-week interim sacrifice, focal necrosis of the liver was observed in females at incidences of 1, 0, 0, 3 and in males at 1, 1, 1, 0 in the control, low-, mid-, and high-dose groups, respectively. The grade of the lesion was very slight or

slight in all cases and was not considered compound-related. No indication of compound-related focal hepatocyte necrosis was evident in rats of the 2-year main study.

There were no compound-related effects in organ weights or gross lesions in males and females of the main 2-year study.

There were no compound-related nonneoplastic lesions. Focal myocardial fibrosis was increased in treated females in comparison to controls. The incidences of this lesion were 5, 4, 8, 8, and 11 in control I, control II, low-, mid-, and high-dose females. The grades of the lesion were very slight to slight and were comparable among groups. Additionally, the occurrence of this lesion was primarily in the early deaths and early sacrificed animals. The earliest occurrence of the lesion was recorded at days 420, 465, 310, 442, and 449 in control I, control II, low-, mid-, and high-dose groups. There was no relationship to treatment.

There were no compound-related benign or malignant neoplasms in male or female rats. Additionally, there were no decreases in latency.

The most common tumors in male rats were in the pituitary, liver, pancreas, and thyroid.

The type and incidences of the commonly occurring tumors in male rats are shown below.

	Males				
mg/kg/day	0	0	0.75	1.5	2.0
No. Examined	50	50	50	50	50
HC* Adenoma	3	4	7	6	6
HC* Carcinoma	3	0	2	1	3
Thyroid C-Cell Adenoma	5	4	6	7	1
Pancreas, Islet - Adenoma	3	8	3	8	5
Pituitary - Adenoma	17	21	18	24	18
Pituitary - Adenocarcinoma	4	6	7	8	8

*Hepatocellular

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The most commonly occurring tumors in female rats were in the mammary gland and pituitary. The types and incidences of these tumors are shown below.

	Females				
mg/kg/day	0	0	0.75	1.5	2.0
No. Examined	50	50	50	50	50
Mammary Gland					
Fibroadenoma	19	14	17	10	22
Adenocarcinoma	8	11	9	8	9
Adenoma	7	8	7	5	5
Pituitary					
Adenoma	31	33	33	37	27
Adenocarcinoma	15	10	7	5	10

Conclusion:

The oncogenic potential is negative. The systemic NOEL is 1.5 mg/kg/day, the mid dose. The LEL is 2.0 mg/kg/day, the high dose. At this level, there were four females and two males with treatment-induced tremors. An additional female in the mid-dose group also had tremors, but this animal consumed about 2.5 mg/kg/day of abamectin during this period (based on actual food consumption and body weight data). There were no compound-related pathological lesions to correlate with the tremors. The high dose is also the MTD for both sexes, since tremors were observed in both sexes.

Classification: Core-Minimum